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09/287,500	04/07/1999	JOHN C. LEE	STK-1-DIV-3	6377

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JAMES F HALEY
FISH & NEAVE
1251 AVENUE OF THE AMERICAS
NEW YORK, NY 10020

EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	24

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/287,500	LEE ET AL.	
	Examin r	Art Unit	
	David S Romeo	1647	

-- Th MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-73,102 and 106-122* is/are pending in the application.

4a) Of the above claim(s) *70,72,73 and 118-122* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69,71,102 and 106-117* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *69-73,102 and 106-122* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet.*

Continuation of Attachment(s) 6). Other: pages 71-73 of the as-filed specification.

DETAILED ACTION

The amendment filed April 2, 2003 has been entered. Claims 69-73, 102, 106-122 are pending.

Applicant's election with traverse of group I, claims 69-73 and 102 to the extent that they are drawn to a method of inducing local tissue formation comprising implanting a morphogenic protein and IGF-I, in Paper No. 21 is acknowledged. The traversal is on the ground(s) that the MPSFs are recited as members of a Markush group, which is made up of only four members. Four members is "sufficiently few," according to MPEP § 803.02. Therefore, the examiner must examine all members of the Markush group. This is not found persuasive because since the decisions in In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. Although IGF-I, hydrocortisone, insulin, and PTH share a common utility in that they are disclosed as MPSFs, they do not share a substantial structural feature disclosed as being essential to that utility. Indeed, hydrocortisone is not even a polypeptide. Furthermore, IGF-I, hydrocortisone, insulin, and PTH are all classified separately. Separate classification (i.e., class and subclass) of

distinct inventions is sufficient to establish a prima facie case that the search and examination of the plural inventions imposes a serious burden upon the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 118-122 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 21.

Applicant's election of the species bone defect locus, the species fracture, and the species BMP-7 in Paper No. 21 is acknowledged. Claims 70, 72, 73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 69, 71, 102, 106-117 are being examined to the extent that they read upon a method of inducing local tissue formation comprising implanting a morphogenic protein and IGF-I, and the species bone defect locus, the species fracture, and the species BMP-7.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 102

Claims 69, 71, 106-112, 114, 115 are rejected under 35 U.S.C. 102(b) as being anticipated by Wang (b7).

Wang teaches that BMP-2 (wherein BMP is bone morphogenic protein) may be used to induce bone formation, provides pharmaceutical compositions containing a therapeutically effective amount of a BMP-2 in a pharmaceutically acceptable vehicle or carrier, the compositions further include at least one other therapeutically useful agent such as the BMP proteins BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, the compositions may also include an appropriate matrix for instance, for supporting the composition and providing a surface for bone growth, administration of a BMP-2 in conjunction with at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, and the administration of a BMP-2 with other growth factors (paragraph bridging columns 2-3). It is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors. Further therapeutic methods and compositions of the invention therefore comprise a therapeutic amount of at least one BMP-2 with a therapeutic amount of at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7. Such combinations may comprise separate molecules of a BMP or heteromolecules comprised of different BMP moieties. For example, a method and composition of the invention may comprise a disulfide linked dimer comprising a BMP-2 and another "BMP". Further, BMP-2s, such as BMP-2A and BMP-2B, may be combined with other agents beneficial to the treatment of the bone defects. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF) or IGF-I (column 6, lines 5-57; column 7, lines 7-42). Wang also teaches that a protein of the present invention has application in the healing of bone fractures (paragraph bridging columns 5-6).

Applicant argues that Wang does not teach that the MPSF must be present at an effective concentration to "synergistically" stimulate the tissue inductive capacity of the morphogenic protein. Applicant's arguments have been fully considered but they are not persuasive. As indicated above, Wang teaches that it is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors. Wang further teaches, as indicated above, that BMP-2s, such as BMP-2A and BMP-2B, may be combined with other agents beneficial to the treatment of the bone defects. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF) or IGF-I. If BMP-2 may act in concert with or perhaps synergistically with a growth factor such as IGF-I, as taught by Wang, then by necessity the IGF-I present at an effective concentration to "synergistically" stimulate the tissue inductive capacity of the morphogenic protein.

Claim Rejections - 35 USC § 103

Claims 69, 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (b7) in view of Kuberasampath (n11).

Wang teaches that BMP-2 (wherein BMP is bone morphogenic protein) may be used to induce bone formation, provides pharmaceutical compositions containing a therapeutically effective amount of a BMP-2 in a pharmaceutically acceptable vehicle or carrier, the compositions further include at least one other therapeutically useful agent such as the BMP proteins BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, the compositions may also include an appropriate matrix for instance, for supporting the composition and

providing a surface for bone growth, administration of a BMP-2 in conjunction with at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, and the administration of a BMP-2 with other growth factors (paragraph bridging columns 2-3). It is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors. Further therapeutic methods and compositions of the invention therefore comprise a therapeutic amount of at least one BMP-2 with a therapeutic amount of at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7. Such combinations may comprise separate molecules of a BMP or heteromolecules comprised of different BMP moieties. For example, a method and composition of the invention may comprise a disulfide linked dimer comprising a BMP-2 and another "BMP". Further, BMP-2s, such as BMP-2A and BMP-2B, may be combined with other agents beneficial to the treatment of the bone defects. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF) or IGF-I (column 6, lines 5-57; column 7, lines 7-42). Wang also teaches that a protein of the present invention has application in the healing of bone fractures (paragraph bridging columns 5-6). Wang (b7) does not teach a carrier comprising heparin.

Kuberasampath (n11) teaches a device comprising a carrier comprising heparin (page 5, full paragraph 1; paragraph bridging pages 5-6). Kuberasampath (n11) does not teach a method of administering a composition comprising a carrier, a morphogen and IGF-I.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer a composition comprising a carrier, a morphogen

and IGF-I, as taught by Wang (b7), and to modify that teaching by administering a composition comprising a carrier comprising heparin, as taught by Kuberasampath (n11), with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings in order to induce the formation of endochondral bone in a mammalian host in a shape conforming substantially to the shape of the device or in order to use the device as a surface coating for implantable prosthetic devices to promote cellular ingrowth. The invention is prima facie obvious over the prior art.

Applicant argues that Wang does not teach or suggest synergism; that Kuberasampath does not teach that synergisms exists between MPSFs and morphogenic proteins. Applicant's arguments have been fully considered but they are not persuasive. As indicated above, Wang teaches that it is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors. Wang further teaches, as indicated above, that BMP-2s, such as BMP-2A and BMP-2B, may be combined with other agents beneficial to the treatment of the bone defects. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF) or IGF-I. If BMP-2 may act in concert with or perhaps synergistically with a growth factor such as IGF-I, as taught by Wang, then by necessity the IGF-I present at an effective concentration to "synergistically" stimulate the tissue inductive capacity of the morphogenic protein. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

New Formal Matters, Objections, and/or Rejections:

Specification

The disclosure is objected to because of the following informalities: The specification is objected to because portions of pages 71-73 are missing. See the attached pages of the as-filed specification that comprise the missing portions.

Appropriate correction is required.

The application is not fully in compliance with the sequence rules, 37 C.F.R. § 1.821-1.825. Specifically, the specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See, for example, pages 24-26. This is not meant to be an exhaustive list of places where the specification fails to comply with the sequence rules. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. The application cannot issue until it is in compliance. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply with the sequence rules. Amino acid sequences with 4 or more residues, at least 4 of which are specifically defined, must comply with the sequence rules. Sequence identifiers can also be used to discuss and/or claim parts or fragments of a properly presented sequence. For example, language such as "residues 14 to 243 of SEQ ID NO:23" is permissible and the fragment need not be separately presented in the "Sequence Listing."

Correction is required.

Claim Rejections - 35 USC § 112

Claims 69, 71, 102, 106-117 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is being made in combination with the prior art rejections because Applicant's disclosure discloses no more, and perhaps even less, than the prior art with respect to the claimed invention.

The claims are directed to or encompass the induction of any and/or all local tissue formation, or the induction of endochondral or intramembranous bone, or cartilage, or tendon/ligament-like, neural, or neural like, soft tissue with a morphogen and synergistic enhancement of the morphogen's tissue induction with an MPSF. The only working example in the present specification is the induction of alkaline phosphate activity in FRC cells. There is nothing in the prior art of record or in the present specification that establishes a nexus between the induction of alkaline phosphate activity in FRC cells and the induction of any and/or all local tissue formation and/or the synergistic stimulation thereof. Furthermore, the use of in vitro assay systems has proven not to be predictive of bone formation in vivo. See Wozney (U), paragraph bridging pages 726-727. This is also obvious from the specification's disclosure (page 39, full paragraph 2) wherein the data summarized in FIG. 12 indicate that TGF-β is not a MPSF in combination with OP-1 in the AP activity assay in FRC cells in vitro. TGF-β alone did

not stimulate AP activity. TGF-β (0.05-3.0 ng/ml) did not exhibit any synergistic effect with OP-1 on AP activity. However, TGF-β and BMP synergize in promoting formation of endochondral bone in vivo. See Ogawa (u11), page 14233, paragraph bridging columns 1-2. Thus, the in vitro assay of AP activity is not predictive of synergistic enhancement of bone formation in vivo. Furthermore, Vukicevic (x7) teaches that OP-1 promotes cell condensations and tubulogenesis in metanephric mesenchyme but BMP-2, a closely related member of the TGF-β superfamily, and TGF-β1 had no effect (page 9023, paragraph bridging columns 1-2). Vukicevic establishes that closely related members of the TGF-β superfamily have unpredictable effects.

Furthermore, the claims encompass the regeneration of permanent cells that are retained throughout adult life and seem never to divide and which cannot be replaced if lost, such as almost all nerve cells, the muscle cells of the heart, the auditory hair cells of the ear, and the lens cells of the eye. See Alberts (z7), pages 1142, last full paragraph, and pages 1144-1145. Although most permanent cells renew their parts, the claims encompass the growth of permanent cells, which cannot be replaced if lost. The specification fails to provide guidance for, or working examples of, regenerating permanent cells, which cannot be replaced if lost. Nerve regeneration across a gap is not commensurate with the scope of the claimed invention because the claims are not limited to nerve regeneration across a gap and encompass the regeneration of entire cells.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, and the unpredictability in the art it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

Applicant argues that neurons can be regenerated if damaged and that example 13 of the present specification is similarly described in WO 95/05846; that the prior art demonstrates that neural regeneration does occur; all that is required is to use the recited MPSF with any BMP with known inductive capacity in a tissue; that Applicant need not demonstrate the operativeness of all species in the claimed genus. Applicant's arguments have been fully considered but they are not persuasive.

In contrast to inducing dendritic growth (Liam) or nerve trunk regeneration (Derby or Lunborg), the present claims encompass the induction of tissue where previously there was none.

It is unclear what NGF facilitation of regeneration across nerve gaps (Derby) has to do with a morphogenic or osteogenic protein. Liam makes it clear that the actions of OP-1 are distinct from those of NGF (page 603, left column).

Katagari teaches that BMP-2 inhibited the muscle phenotype and induced the osteoblasts phenotype, indicating that BMP-2 inhibits local tissue formation, in contrast to the present claims which require "inducing local tissue formation." Furthermore, osteoblasts, chondrocytes, myocytes, and adipocytes (Katagari) are not neuronal cells or tissue.

It is unclear how the inhibitory effect of BMP-2 on myogenic differentiation in myoblasts (Yamaguchi) supports "inducing local tissue formation," as required by the present claims.

Lyons suggests that BMP-2A plays multiple roles in morphogenesis and pattern formation in the vertebrate embryo (Abstract). Jones suggest that BMP-4 and Vgr-1 play key roles in the initial stages of neurogenesis and organogenesis during murine

[embryonic] development. Jones (abstract) also suggest distinct roles for BMP-4 and Vgr-1 during embryonic development. Maéno examines the biological effects of endogenous bone morphogenetic protein 4 (BMP-4) on embryonic development of Xenopus laevis (Abstract). King mainly deals with the embryonic expression of BMP-5. However, as noted by Nathan (y7) many cytokines that subserve familiar functions postnatally play different or unknown roles embryologically and given the amino acid sequence of a cytokine and any of its actions one cannot predict when or where it will do what else (page 981, paragraph bridging columns 1-2). Lyons also suggest that BMP-2A may have different effects depending on whether it is part of a homodimer or heterodimer (paragraph bridging pages 836-837), indicating a lack of predictability in the art.

Ozkaynak discloses mRNA expression of BMP-3, BMP-4, BMP-5, and BMP-6/Vgr-1 in lung or liver of young and adult mice (Abstract). King discloses that BMP-5 is expressed in lung, heart, and liver (Figure 2). Schluesener suggests that aberrant expression of BMPs might contribute to smooth muscle cell migration, proliferation, tissue reorganization and macrophage attraction (Abstract). However, Ozkaynak, King, and Schluesener do not disclose that each of these BMPs induces "local tissue formation" or that they synergize with a MPSF.

According to MPEP § 2164.03 (Relationship of Predictability of the Art and the Enablement Requirement), the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention,

how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. This is because it is not obvious from the disclosure of one species, what other species will work. In the present case there is a lack of predictability in the art and it is not obvious from the present specification's disclosure that OP-1 and IGF-I will work in vivo, as required by the present claims. It is

also not obvious from the present specification's disclosure which morphogenic or osteogenic protein in combination with IGF-I will result in the synergistic enhancement of a tissue's induction. The only working example in the present specification is the induction of alkaline phosphate activity in FRC cells. There is nothing in the prior art of record or in the present specification that establishes a nexus between the induction of alkaline phosphate activity in FRC cells and the induction of any and/or all local tissue formation and/or the synergistic stimulation thereof. Furthermore, the use of in vitro assay systems has proven not to be predictive of bone formation in vivo. See Wozney (U), paragraph bridging pages 726-727. This is obvious by the specification's disclosure (page 39, full paragraph 2) wherein the data summarized in FIG. 12 indicate that TGF-β is not a MPSF in combination with OP-1 in the AP activity assay in FRC cells in vitro. TGF-β alone did not stimulate AP activity. TGF-β (0.05-3.0 ng/ml) did not exhibit any synergistic effect with OP-1 on AP activity. However, TGF-β and BMP synergize in promoting formation of endochondral bone in vivo. See Ogawa (u11), page 14233, paragraph bridging columns 1-2. Thus, the in vitro assay of AP activity is not predictive of synergistic enhancement of bone formation in vivo. One skilled in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains.

Claims 69, 71, 102, 107-110, 115, 116 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. Claims 69, 71, 102, 107-110, 115, 116 recite the term "morphogenic" or "osteogenic" protein. These terms encompass a genus of polypeptides.

According to the specification, the term "morphogenic protein" means osteogenic, BMP and BMP-related proteins (paragraph bridging pages 2-3); morphogenic proteins such as OPs and BMPs, including variants and mutants with increased bioactivities (paragraph bridging pages 3-4). The term "morphogenic protein" refers to a protein having morphogenic activity (page 8, full paragraph 4); a morphogenic protein may be prepared synthetically for use in concert with a MPSF to induce tissue formation. Morphogenic proteins prepared synthetically may be native, or may be non-native proteins, i.e., those not otherwise found in nature (page 23, full paragraph 4): the synthetic morphogenic protein ... of this invention comprises a protein which comprises a sequence sufficiently duplicative of the sequence of COP5 or COP7 (page 25, full paragraph 2).

According to the specification, the term "osteogenic protein" means a morphogenic protein that is capable of inducing a progenitor cell to form cartilage and/or bone (page 8, full paragraph 1). The natural osteogenic proteins of this invention ... may include forms having varying glycosylation patterns, varying N-termini, and active truncated or mutated forms of native protein (page 15).

The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to members of the genus. Thus, the scope of the claim includes numerous

structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the BMP subfamily of the TGF-β superfamily alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claims 69, 71, 102, 107-110, 115, 116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 69, 71, 102, 107-110, 115, 116 are indefinite because they recite the term "morphogenic" or "osteogenic" protein. Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "morphogenic" or "osteogenic" protein an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element. The metes and bounds are not clearly set forth.

Claim 110 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 110 is indefinite since it is not clear what applicant intends to cover by the recitation "tendon/ligament-like" or "neural-like" tissue. It is unclear from the specification what applicant intends to cover by the recitation of "tendon/ligament-like" or "neural-like" tissue. The metes and bounds are not clearly set forth.

Claims 116, 117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 116, 117 recite the limitation "pharmaceutical composition." There is insufficient antecedent basis for this limitation in the claim.

Claims 69, 71, 102, 106-117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 69, 71, 102, 106-117 are indefinite because they recite the term "local tissue formation." Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "local tissue formation" an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element. It is unclear if appropriate or ectopic tissue is formed. The metes and bounds are not clearly set forth.

Claim Rejections - 35 USC § 103

Claims 69, 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (b7).

Wang teaches that BMP-2 (wherein BMP is bone morphogenic protein) may be used to induce bone formation, provides pharmaceutical compositions containing a therapeutically effective amount of a BMP-2 in a pharmaceutically acceptable vehicle or carrier, the compositions further include at least one other therapeutically useful agent such as the BMP proteins BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, the compositions may also include an appropriate matrix for instance, for supporting the composition and providing a surface for bone growth, administration of a BMP-2 in conjunction with at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7, and the administration of a BMP-2 with other growth factors (paragraph bridging columns 2-3). It is expected that a BMP-2 may act in concert with or perhaps synergistically with other related proteins and growth factors. Further therapeutic methods and compositions of the invention therefore comprise a therapeutic amount of at least one BMP-2 with a therapeutic amount of at least one of BMP-1, BMP-3, BMP-5, BMP-6 and BMP-7. Such combinations may comprise separate molecules of a BMP or heteromolecules comprised of different BMP moieties. For example, a method and composition of the invention may comprise a disulfide linked dimer comprising a BMP-2 and another "BMP". Further, BMP-2s, such as BMP-2A and BMP-2B, may be combined with other agents beneficial to the treatment of the bone defects. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors

(TGF-α and TGF-β), and insulin-like growth factor (IGF) or IGF-I (column 6, lines 5-57; column 7, lines 7-42). Wang also teaches that a protein of the present invention has application in the healing of bone fractures (paragraph bridging columns 5-6). Wang (b7) is silent with respect to the specific dosages recited in claim 116. However, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. The invention is prima facie obvious over the prior art.

Claims 69, 113, 117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (b7), as applied to claim 69 above, and further in view of Kuberasampath (e7) and Reddi (V).

Wang is silent with respect to the "synergistic" combination of BMP-7 and IGF-I.

Kuberasampath provides methods and compositions for inhibiting loss of bone mass, and/or for stimulating bone formation in mammals, particularly humans which includes administering to the individual a therapeutically effective morphogen in an amount and for a time sufficient to inhibit the loss of bone mass, and/or to increase bone mass in the individual. (column 3, lines 15-25). The morphogens may be administered together with other "co-factors" known to have a beneficial effect on bone remodeling, including IGF-I (column 4, lines 58-65). OP-1 is a useful morphogen (paragraph bridging columns 4-5).

Reddi teaches that the initiation of bone formation by osteogenin or BMPs is promoted by PDGF, TGF-β, IGF-1 and -2, and FGF (page 34, column 2).

Kuberasampath and Reddi are silent with respect to the "synergistic" combination of BMP-7 and IGF-I. However, the fact that BMP-2 may act in concert with or perhaps synergistically with a growth factor such as IGF-I, the fact that the initiation of bone formation by BMPs is promoted by IGF-1, that fact that OP-1 is a useful morphogen, and the fact that OP-1 may be administered together with other "co-factors," such as IGF-I, known to have a beneficial effect on bone remodeling, creates a reasonable expectation that the combination of OP-1 and IGF-I is synergistic. With respect to the specific dosages recited in claim 117, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. The invention is prima facie obvious over the prior art.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 69, 71, 102, 106-117 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,048,964. Although the conflicting claims are not identical, they are not patentably distinct from each other because administering to a cell, as recited in the patent, encompasses administering to a mammal, as recited in claim 12 of the patent and as

recited in the present claims. moreover, "tissue inductive activity," as recited in the patent, appears to cover the same thing as "local tissue formation," as recited in the present claims. Furthermore, claims 11 and 15 of the patent limit the invention to IGF-I, as recited in the present claims. Both sets of claims recite the same morphogenic factors in the same, similar, or overlapping concentrations.

Claims 69, 71, 102, 106-117 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 30 of U.S. Patent No. 5948428. Although the conflicting claims are not identical, they are not patentably distinct from each other because an agent that increases IGF-I bioactivity, as recited in the patent, is IGF-I, as recited in the present claims.

Conclusion

No claims are allowable.

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DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
NOVEMBER 16, 2003